IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Richmond Division

LISA and SETH SYKES, individually
and as parents and natural guardians of
WESLEY ALEXANDER SYKES,
a minor child,

Plaintiffs,

v. Case No. 3:07CV660

BAYER PHARMACEUTICALS CORPORATION,

Defendant.

PLAINTIFFS' MEMORANDUM IN OPPOSITION TO
DEFENDANT'S MOTION FOR JUDGMENT ON THE PLEADINGS

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Plaintiffs file this memorandum in opposition to the Motion for Judgment on the Pleadings pursuant to Federal Rule of Civil Procedure 12(c) filed by Defendant Bayer Pharmaceuticals Corporation (hereinafter "Bayer").

I. INTRODUCTION

It is Plaintiffs' position that their claims that Bayer's (1) failure to adequately test its immune globulin blood product (HypRho-D) given to Mrs. Sykes before Wesley was born; and (2) failure to properly design and manufacture its HypRho-D constitute negligence and breach of warranty under Virginia law. Plaintiffs further contend that a claim for failure to provide adequate warnings should also be allowed under Virginia law, and, contrary to Judge Stegel's opinion, should not be preempted under federal law. Finally, Plaintiffs have moved for leave of court to amend their complaint and for leave to add additional defendants. It is respectfully requested that these motions be ruled on before any decision is made about the adequacy of the pleadings to set forth actionable claims under Virginia law. A Motion for Judgment on the Pleadings should not be granted, particularly since Plaintiffs have not been allowed any discovery in the Eastern District of Pennsylvania, and discovery has just begun in this Court.

A. *Brief Summary of the Parties' Positions*

Bayer's positions are simply stated:

1. The FDA made us put Thimerosal, a preservative containing mercury, in our HypRho-D; and
2. We couldn't make the HypRho-D received by Mrs. Sykes without violating FDA regulations and our license with the FDA.

Thus, Bayer contends, the case should be dismissed at this early stage because FDA made it injure Mrs. Sykes, and it had no choice to do otherwise. For the reasons stated below, Bayer's premise is specious and totally inconsistent with the FDA's position that the FDA relies upon information provided by the manufacturers, and that Bayer had a choice to use a different and safer preservative. Bayer's first contention above is totally untrue. The second is also false with regard to "FDA regulations", and, with regard to violating their "license with the FDA", Bayer is saying, "Once we committed the negligent actions (improper design and manufacture of its product), and once we got away with it, we didn't want to do anything to jeopardize our ability to continue manufacturing and selling defective product."

B. *Plaintiffs' Claims Properly Stated*

Plaintiffs allege the following claims under Virginia law:[1]/

1. Bayer's negligence and breach of warranties resulted in a defectively designed product;
2. Bayer's negligence and breach of warranties resulted in a defectively manufactured product; and
3. Bayer's negligence and breach of warranties resulted in a product that was unreasonably dangerous and lacked adequate warnings about the product's safety and the alternatives that were then available to the Plaintiff, Lisa Sykes.

Plaintiffs allege under Virginia law that Bayer improperly designed and manufactured HypRho-D. At the time HypRho-D was designed and manufactured for use by Mrs. Sykes, there was overwhelming evidence in the medical literature that Thimerosal was (1) highly neurotoxic,

[1] These claims are more clearly set forth in the Amended Complaint which Plaintiffs seek leave of Court to file in this matter.

carcinogenic, mutagenic, and NOT safe; (2) Thimerosal was an ineffective preservative; (3) other better preservatives were available; and (4) by utilizing more sterile conditions in the manufacturing process, a product could be made without any preservative, and the FDA would allow a waiver of the preservative requirement under such circumstances. Bayer had knowledge of all of these facts, and chose profits over safety.

At the time the HypRho-D administered to Mrs. Sykes was manufactured, Bayer knew that its product was unreasonably dangerous, and it knew that better alternatives were available (including products with non-mercury preservatives and products without any dangerous preservatives at all), and it failed to provide adequate warnings to the doctors who administered their product and the women who received it, including Mrs. Sykes and her doctor.

When Bayer first designed and sought approval for its HypRho-D, it had performed NO safety tests for the use of Thimerosal. It knew that the manufacturer of Thimerosal, Eli Lilly, made flawed and inaccurate claims that Thimerosal was safe. Plaintiffs believe and therefore allege that Bayer relied on safety studies conducted by another manufacturer in Canada when it presented their product to the FDA for licensing, knowing full well that the Canadian product did not contain Thimerosal. Plaintiffs do not allege, as Bayer suggests, a "fraud on the agency" claim. Plaintiffs do claim, however, that Bayer cannot hide behind FDA regulations and an FDA license, when they obtained their approval knowingly using false information. Nor can they claim their warnings were adequate because the FDA said so, when they knew the warnings were not adequate. Plaintiffs are not claiming that Bayer defrauded the FDA, but rather that Bayer cannot defend the claims of negligence and breach of warranties by simply asserting, falsely, that the FDA made it do what it did.

As will be seen below, the FDA relies on information provided by manufacturers. Bayer

seems to be saying it had no choice and had to rely on what the FDA made it do. For those who remember José Jiménez[2] on the Ed Sullivan show year ago, the line, "Is not my job," seems appropriate. Let's be clear: The job of properly designing and manufacturing a product belongs to Bayer, and failure to warn is the responsibility of Bayer. Just because Bayer was were able to fool the policeman and get away with negligent actions does not mean it's not responsible for its own wrongdoings.

Defendant Bayer spends nine pages describing how important the FDA is in the licensing of its product. Plaintiffs agree that an FDA license was necessary to manufacture and market HypRho-D. What Defendant would have this Court believe is that, regardless of its misconduct in designing, applying for a license, manufacturing, marketing and selling HypRho-D, as long as the FDA put its stamp of approval on the product, then there can be no further inquiry into whether Bayer was negligent or breached any warranties under Virginia law. Mere licensure of a product, which was not required to contain the dangerous preservative Thimerosal, does not confer the broad immunity sought by Bayer.

Plaintiffs contend that Bayer's conduct was negligent and breached warranties, all as set forth in the proposed amended complaint that Plaintiffs seek leave of Court to file herein. Specifically, the following information is provided in support of Plaintiffs' contentions.

II. FACTS THAT SUPPORT PLAINTIFFS' STATE LAW CAUSES OF ACTION

A. Drug manufacturers have an absolute non-dischargeable duty to prove each of their drugs is safe and effective. A manufacturer cannot transfer this responsibility to the FDA. By regulation, FDA must rely on information provided to it by Bayer in determining whether the

[2] Fictional character created by comedian Bill Dana, who, whenever he was stumped by a question, would shrug and say, "Ees not my job!"

product is safe and effective and therefore can be licensed.[3]

B. This non-dischargeable duty of the manufacturer extends to every "component" of a drug under 21 U.S.C § 321(g)(1)(D)

> 21 U.S.C. Sec. 321(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and **(D)** articles intended for use as a component of any article specified in clause (A), (B), or (C).

C. To prove the drug is safe and effective, drug manufacturers must first prove that the component is "safe" and "effective" according to the established current good manufacturing practice (CGMP) **minimums**, including, *at a minimum*, the applicable regulations set forth in **21 C.F.R. Parts 210** and **211** as well as those regulations incorporated by reference therein.

D. Since Bayer's duties are absolute and non-dischargeable, the manufacturer may NOT rely on the representations made in the literature or by an FDA administrator, including the granting of a license or approval by said administrator, but MUST, at a minimum, conduct the studies required to prove the drug is safe and effective.

E. In *Berkovitz v. USA*,[4] the Supreme Court unanimously found that an administrator has no discretion when it comes to a clear law or regulation requiring some specific action. With

[3] See attached Exhibit A, which is a pleading filed by the FDA in another matter, paying particular attention to the highlighted sections.
[4] Berkovitz v. USA, 486 U.S. 531 (1988).

respect to the issue of a drug that failed to meet its requirements, but was "released" by the administrative action of an FDA official, footnote 10 in *Berkovitz* is particularly revealing:

> FN10 Even the Government conceded at oral argument that the DBS has no discretion to issue a product license without an examination of the product and a determination that the product complies with regulatory standards. The transcript reads:
> "QUESTION: [Supposing the DBS] did not make any examination of the application at all, or any determination other than some papers have been filed and I will now issue the license.
> "Would that comply with the regulation?
> "[COUNSEL]: No, it would not comply with the regulation.
> "QUESTION: It would violate a mandatory duty..., wouldn't it?
> "[COUNSEL]: In the extreme instance you are talking about ..., it would definitely violate that regulation." Tr. of Oral Arg. 34-35.

F. Factually, Bayer has provided NO evidence that it provided the safety and effectiveness proofs required by law for this product. It is Plaintiffs' belief and contention that it has NO such evidence, and it cannot satisfy this requirement by simply saying a "license was issued."

G. In 1973, the general and specific requirements for biological products including sera (such as Bayer's HypRho-D) that were set forth in Title 42 of the Code of Federal Regulations (C.F.R.) were re-codified in Parts 600 through 680 of Title 21 of the C.F.R.

H. 21 C.F.R. Parts 210 and 211 set forth, respectively, the requirement <u>minimums</u> for "CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS: GENERAL" and "CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS" and include biological products by reference as follows [emphasis added]:

8.1. § 210.1 Status of current good manufacturing practice regulations.

(a) **The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety**, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) **The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug,** as well as the person who is responsible for the failure to comply, **shall be subject to regulatory action.**

(c) …

8.2. § 210.2 Applicability of current good manufacturing practice regulations.

(a) **The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use;** and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act)**; shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.**

(b) **If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 of this chapter, in parts 600 through 680 of this chapter,** and in part 1271 of this chapter, **and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.**

8.3. 21 C.F.R. Part 211 Subpart A—General Provisions

§ 211.1 Scope.

(a) **The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.**

(b) **The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use;** and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); **supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter,** or in part 1271 of this

chapter, **the regulation specifically applicable to the drug product in question shall supersede the more general.**

Specific requirements with which the Defendant Bayer has failed to provide proof that their biological drug product complies include, but are not limited to, compliance with:

9.1 PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Section Contents
Subpart B—General Provisions
§ 610.15 Constituent materials.

(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. **Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient**, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:

(1) 0.85 milligrams if determined by assay;

(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or

(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2 of this chapter).

9.2. PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Section Contents

Subpart J—Immune Globulin (Human)

§ 640.103 The final product.

(a) Final solution. **The final product shall be a 16.5 ±1.5 percent solution of globulin containing** 0.3 molar glycine and **a preservative**.

(b) …

I. The Defendant Bayer has provided no proof that they even made an effort to comply with 21 C.F.R. Sec. 610.15(a) regarding the proof of safety of the "preservative" they choose to use to the minimum standard required, namely: "Any preservative shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient," a standard that the Defendant admits is applicable to the product. Instead of offering any proof of safety, Defendant Bayer's Exhibit E offers an FDA April 28, 2006 web page discussing "Thimerosal in Vaccines, a different product category than the globulin product in question, and a "MEMORANDUM" titled: "Use of Thimerosal in Biologics Production" that establishes no official policy, does not provide any proof of safety for the Thimerosal in the Defendant's product, and, in any case, cannot be used to discharge the Defendant's absolute non-dischargeable duty to prove by appropriate testing using the drug product formulation that the drug was sufficiently nontoxic to both the mother and the fetus at 28 weeks gestation.

J. Notwithstanding any FDA action, Bayer failed to provide the proof that the preservative used in Bayer's drug product met the clear CGMP requirement minimum for a preservative that is "sufficiently nontoxic" set forth in **21 C.F.R. 610.15(a)** renders all of the lots of their drug product adulterated under **21 U.S.C. 351(a)(2)(B)**, which clearly requires that the manufacturer must comply with the direct and indirect (those included by reference in **21 CFR Parts 600** through **680**) CGMP minimums requirements set forth in 21 CFR Parts 210 and 211. This is the case because ***Berkovitz*** clearly disallows any administrative discretion whenever there

is a clear CGMP minimum that, *as the drug manufacturer*, Defendant Bayer has an absolute non-dischargeable duty to meet but has, *for whatever reason*, knowingly failed to meet.

K. Thus, all lots of Bayer's HypRho-D are adulterated drugs under 21 U.S.C. Sec. 351(a)(2)(B), and, based on this factual reality alone, the Plaintiffs are entitled to present this evidence – that the product is adulterated under the law – before a jury.

L. With respect to the "and a preservative" requirement set forth in 21 C.F.R. Sec. 640.103(a), nowhere does this regulation require that: (a) the preservative must be 0.01% Thimerosal, or (b) the preservative need NOT meet the "preservative shall be sufficiently nontoxic …" CGMP requirement minimum set forth for safety in 21 C.F.R. Sec. 610.15(a).

M. Based on all of this, Bayer's Motion for Judgment on the Pleadings should be denied, and the Sykes should be allowed to conduct discovery to prove definitively that HypRho-D was an adulterated drug and that Defendant undertook insufficient toxicity testing to prove that the preservative used was sufficiently nontoxic.

N. With regard to the labeling requirements for this product, disclosure of the details regarding the FDA-approved preservative also is highly regulated by the FDA. 21 C.F.R. § 610.6l(e) (biologic's label must list "[t]he preservative used and its concentration"). Here, the FDA-approved package insert in effect when Mrs. Sykes was administered HypRho-D advised physicians that it contained "80-l20 ug/mL Thimerosal (a mercury derivative), as measured by mercury assay," and warned that HypRho-D "should be given with caution ... to patients who are known to have had an allergic response to thimerosa1." Rho(D) Immune Globulin (Human), USP -HypRho-D Full Dose Package Insert (Rev. October 1995). This was the information the

FDA required Bayer to supply about thimerosal. Further, the FDA-mandated Pregnancy Category C warning advised physicians that it is "not known whether [HypRho-D] can cause fetal harm when administered to a pregnant woman" and therefore it "should be given to a pregnant woman only if clearly needed." Rho(D) Immune Globulin (Human), USP -HypRho-D Full Dose Package Insert (Rev. October 1995); 21 C.F.R. § 201.57(c) (requiring verbatim warning). A manufacturer may not include a warning on its label unless there is "reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.57(e).

O. In the case of Thimerosal, Bayer has withheld information regarding evidence establishing its toxicity to the developing fetus when administered *in utero*. It is well established from toxicologically appropriate studies that Thimerosal, and its ethylmercury and inorganic mercury breakdown products are toxicity to the developing fetus when exposure occurs *in utero*. Some examples include the following:

> Oharazawa (1968) published a study examining the ability of ethylmercury exposure during pregnancy to induce fetal damage in mice.[5] He observed that injection of ethylmercury during pregnancy significantly reduced the weights of developing fetuses in utero and produced significant increases in fetal malformations and the incidence of unstable chromosomes characterized as polyploidy, chromatid gaps, or fragmented, in comparison to unexposed controls.

> Bakulina (1968) described in study on a human fetal poisoning (emphasis added), "…granosan (ethylmercury chloride) is capable of passing through the placental barrier and penetrating into the fetus, causing in the organs of the latter grave pathological changes. The permeability of the placental barrier for organic mercury compounds finds its confirmation in the presence of mercury in the placenta and organs of the fetus…Breast feeding was found to be conducive to accumulation of mercury in the organism of newborns, since the mothers'

[5] Oharazawa, H. 1968. Effect of ethylmercuric phosphate in the pregnant mouse on chromosome abnormalities and fetal malformation. *J. Jpn. Obstet. Gynecol.* 20:1479-1487.

milk, as a rule, disclosed the presence of this element. A very important point was that fetal intoxication was possible for as long as 3-4 years after the mother poisoned."[6]

Goncharuk (1971) administered an ethylmercury compound to albino rats, and subsequently, these animals were mated.[7] Investigations were made of the sexual cycle, and the viability, physical development and fertility of the progeny of the first and second generations. It was observed that females that had been previously exposed to the ethylmercury compound became pregnant only on the 4th or 5th occasion when they were placed with males when in estrus, whereas non-exposed control females became impregnated on the 1st or 2nd mating. The number of offspring per litter was significantly smaller in the animals treated with the ethylmercury compound than in controls. It was also observed that young rats from mothers that had been previously exposed to the ethylmercury compound died significantly more frequently than controls. Observations of the first-generation progeny revealed a lag in weight growth in comparison to controls, especially during the 1st and 2nd months of extrauterine life. In addition, the first-generation progeny had birth weights that exceeded those of the control group, and studies of skeletal ossification in the young rats revealed a large number of cases with retardation of the appearance and development of ossification centers in bones of the fore and hind paws. Studies of the organs and tissues of the first generation progeny revealed mercury in the stomach and intestine at birth and in the first week of life, apparently on account of the entry of mercury through the placental barrier and by way of their mother's milk. Subsequently, it was noted that the first generation progeny of mothers that had been previously exposed to the ethylmercury compound had significantly reduced fertility in comparison to controls. The second generation progeny had low viability, lagged in their weight growth, and were retarded with respect to ossification in several cases. Finally, it was then observed when mating the second generation progeny that there was a significant decrease in fertility in comparison to the control group.

A later study on pheasants by the Bureau of Sport Fisheries and Wildlife, Patuxent Wildlife Research Center, concluded that ethylmercury compound exposure at a level equivalent to 12.5 ppm mercury was lethal to adult animals and at 4.2 ppm mercury, impaired reproduction in the species.[8] These researchers also reported, "(e)thyl mercury p-toluene sulfonanilide (active ingredient of Ceresan M) at a dietary concentration of 30 parts per million (12.5 parts of mercury per million) was lethal to adult ring-necked pheasants. Egg production and

[6] Bakulina, A. V. (1968). The effect of subacute Granosan poisoning on the progeny. *Sovet Med* 31:60-63.

[7] Goncharuk, G. A. 1971. Experimental investigations of the effect of organomercury pesticides on generative functions and on progeny. *Hyg. Sanit.* 36:40-43.

[8] Spann, J. W., Heath, R. G., Kreitzer, J. F., and Locke, L. N. 1972. Ethyl-mercury-p-toluene-sulfonanilide: lethal and reproductive effects on pheasants *Science* 175:328-330.

survival of third-week embryos were sharply reduced when breeders were maintained on feed containing 10 parts of this compound per million (4.2 parts of mercury per million)…"

Itoi and his colleagues (1972) conducted a series of experiments to evaluate the reproductive toxicity of Thimerosal in rabbits.[9] They observed that injection of increasing doses of Thimerosal (from 0.02 to 0.2% solutions) into pregnant rabbits resulted in significantly increased numbers of dead fetuses (up to 18% of fetuses died following exposure) and increased fetal congenital anomalies (up to 9.1% of fetuses developed congenital anomalies following exposure) in comparison to rabbits injected with physiological saline.

By the early 1970s, researchers developed an overall clinical picture of ethylmercury poisoning in fetuses following large-scale ethylmercury poisoning episodes (Mal'tsev, 1972; Ramanauskayte and Baublis 1973).

Ramanauskayte and Baublis (1973) stated that, after exposure to ethylmercury-treated seeds (emphasis added), "(i)ntrauterine poisoning in infants was observed(.)… (C)hildren on the whole are more susceptible to mercury than adults(.)… Serious functional disorders of the central nervous system, hydrocephalus, cerebral paralysis, and spasms were observed in infants. Toxic encephalomyeloradiculoneuritis with prevalence of the syndromes of lesions of the cerebral cortex, brain stem, cerebellum, myelitis, peripheral neurites, lesions of the motor centers, of the pyramidal tracts, and encephalitis with irregular alpha-rhythm were observed...Epilepsy lasting up to 2 years was observed in 10% of all cases. Prevalence of vegetoneurotic syndromes, tachycardia, bradycardia, arrhythmia, acrocyanosis, liability of the arterial pressure, and reduction of the blood cholinesterase activity were found in older children with chronic poisoning. The lesions of the liver, kidney, heart and gastrointestinal tract were much less pronounced than those of the central nervous system."[10]

Confirming the tremendous danger of ethylmercury compounds to children, Mal'tsev (1972) reported that in cases of children poisoned with ethylmercury, the onset of symptoms usually occurred many weeks following exposure. The first symptoms of ethylmercury poisoning in children included asthenia, fatigability, loss of appetite, followed by nausea, vomiting, liquid feces, abdominal pains, and elevated temperature. Subsequently, the neurological syndrome developed and consisted of symptoms such as ataxia, dysarthria, psychomotor disturbances,

[9] Itoi, M., Ishii, Y., Kaneko, N. 1972. Teratogenicities of antiviral ophthalmics on experimental animals. *Jpn. J. Clin. Ophthal.* 26:631-640.

[10] Ramanauskayte, M. B., and Baublis, P. P. 1973. Clinical picture and treatment of organomercurial pesticide poisoning in children. *Pediatriya Moscow* 35:56-60.

and sleep disturbances. The researcher reported that damage to the nervous system may be irreversible even following low-dose exposure. Mal'tsev (1972) also commented that, upon autopsy of children who died of ethylmercury exposure, degenerative, inflammatory, and necrotic alterations were seen, as well as hemorrhages in the central nervous system, kidney, liver, heart, and intestines. Mal'tsev (1972) also reported that ethylmercury appeared to be the most dangerous to the embryos during the third and four months of pregnancy.[11]

Published in 1977 were the results of a large-scale prospective human epidemiological study (the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke, the US Public Health Service, and the US FDA) on drug exposures during pregnancy and their association with birth defects (Heinonen et al., 1977).[12] This study reported, "(b)etween 1958 and 1965, under the auspices of the National Institute of Neurological and Communicative Disorders and Stroke, a prospective study of over 50,000 pregnancies was undertaken with the main objective of determining whether there are factors during pregnancy or delivery that are related to the risk of cerebral palsy or other neurological outcomes. This study ultimately became known as the Collaborative Perinatal Project. Among many items of data obtained, drug use was recorded during pregnancy, and birth defects identified in the children were recorded subsequently. With the growing realization that drugs are sometimes teratogenic, it became mandatory to evaluate the data from the perspective… The purpose of this book is to present data on drugs used by 50,282 gravidae in relation to birth defects identified in children." The conclusion of these researchers with regard to Thimerosal (emphasis added), "(t)he measure of association presented is a standardized relative risk (SRR) with its 95% confidence limits. The SRR is the ratio of the observed number to the expected number of malformed children. Since the SRR takes into account potential confounding variables, it represents the best estimate of the relationship between a drug and a malformation…Finally, thiomersal…was associated with malformations overall and with uniform malformations." Specifically, it was determined that Thiomersal, another trade name for Thimerosal, exposure during the first 4 months of pregnancy was associated with a statistically significant increased risk (SRR = 2.69) for birth defects.

Digar et al. (1987) expanded the knowledge basis regarding the marked toxicity of Thimerosal to the developing fetus.[13] The researchers reported (emphasis added), "(a) single dose of 0.1 mg of Ethyl-mercury-thiosalicylate (Thimerosal) was injected into the yolk sac of

[11] Mal'tsev, P. V. 1972. Granosan poisoning in children. *Feldsher Akush.* 37:14-16.
[12] Heinonen, O. P., Slone, D., and Shapiro, S. 1977. *Birth Defects and Drugs in Pregnancy*. Littleton: Publishing Sciences Group, Inc.
[13] Digar, A., Sensharma, G. C., and Samal, S. N. 1987. Lethality and teratogenecity of organic mercury (Thimerosal) on the chick embryo. *J. Anat. Soc. India* 36:153-159.

chick embryos…Embryos were collected…It was found that 0.1 mg dose of Thimerosal was lethal in 46.46%. Gross malformations like syndactyly, thinning of the abdominal wall, visceroptosis and scanty feather, during Organogensis as well as in the later period, have been noted in 36.03%...Significant change in the weight of embryo, crown-rump length, body and wing lengths were also observed…However, there was no gross reduction in the size of brain as compared to that of the control. The high incidence of lethality and malformations prove that organic mercury was transmitted from the yolk sac to the embryo. The deleterious effects of mercurials on cells and tissues seem to be due to action on a wide spectrum of enzymes by the organic mercury both on the surface and within the cell. The enzymes particularly involved are – Na – K activated ATPase and also sulfhydryl groups. Goldwater reported that mercury disrupts the normal function of mitochondria and lysosomes."

In addition, manufacturers of Thimerosal included the following information regarding the toxic effects of this compound in their Material Safety Datasheet Sheet (MSDS) prior to Wesley Sykes' in utero exposure to Thimerosal-containing HypoRho-D, and this information was apparently not provided to the FDA or disclosed in the package insert (emphasis added):

***** Eli Lilly & Company's MSDS (Revised: September 1, 1993)*

CALIFORNIA PROPOSITION 65 WARNING

WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.

Human – Occupational Effects, Including Signs and Symptoms, of Exposure: Topical allergic dermatitis has been reported. Thimerosal contains mercury. Mercury poisoning may occur and topical hypersensitivity reactions may be seen. Early signs of mercury poisoning in adults are nervous system effects, including narrowing of the visual field and numbness in the extremities. Exposure to mercury in utero and in children may cause mild to severe mental retardation and mild to severe motor coordination impairment…

Animal Toxicity Data Repeat Exposure…

Reproduction/Developmental: Thimerosal – Increased abortion and fetal death, no malformations. Mercury causes nervous system effects including mild to severe mental retardation and motor coordination impairment…

Mutagenicity: Mutagenic in mammalian cells.

Carcinogenicity: IARC Group 3 – Inadequate evidence of human carcinogenicity. Limited evidence of animal carcinogenicity…

Subsequent, MSDSs prepared by manufacturers of Thimerosal included the following information regarding its toxic effects (emphasis added):

***** Eli Lilly & Company's MSDS (Revised: December 22, 1999)*

Primary Physical and Health Hazards: Skin Permeable. Toxic. Mutagen. Irritant (eyes). Allergen. Nervous System and Reproductive Effects.

Caution Statement: Thimerosal may enter the body through the skin, is toxic, alters genetic material, may be irritating to the eyes, and causes allergic reactions. Effects of exposure may include numbness of extremities, fetal changes, decreased offspring survival, and lung tissue changes…

Effects of Overexposure: Topical allergic dermatitis has been reported. Thimerosal contains mercury. Mercury poisoning may occur and topical hypersensitivity reactions may be seen. Early signs of mercury poisoning in adults are nervous system effects, including narrowing of the visual field and numbness in the extremities. Exposure to mercury in utero and in children may cause mild to severe mental retardation and mild to severe motor coordination impairment. Based on animal data, may be irritating to the eyes…

Chronic Exposure

Thimerosol is a mercuric compound. Toxicity data for thimerosal and mercury are presented.

Target Organ Effects: Thimerosal - Kidney effects (tubule necrosis), lung effects (tissue changes). Mercury - Nervous system effects (insomnia, tremor, anorexia, weakness, headache), liver effects (jaundice, digestive effects (hypermotility, diarrhea).

Other Effects: Thimerosal - Decreased weight gain.

Reproduction: Thimerosal - Decreased offspring survival. Mercury - Changes in sperm production, decreased offspring survival, and offspring nervous system effects including mild to severe mental retardation and motor coordination impairment…

Mutagenicity: Thimerosal - Mutagenic in mammalian cells.

U.S. Regulations

California Proposition 65 (Cancer/Reproductive) - Name on developmental list is mercury and mercury compounds.

Another MSDS provided the following information [emphasis added]:

***** Sigma Chemical Company's MSDS (Valid 11/2002 – 01/2003)*

SECTION 3. - - - - - - - - - - HAZARDS IDENTIFICATION - - - - - - - - -

LABEL PRECAUTIONARY STATEMENTS

HIGHLY TOXIC (USA)

VERY TOXIC (EU)

VERY TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

DANGER OF CUMULATIVE EFFECTS.

MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.

IRRITATING TO EYES, RESPIRATORY SYSTEM AND SKIN.

CALIF. PROP. 65 REPRODUCTIVE HAZARD.

TARGET ORGAN(S):

NERVES

KIDNEYS

SENSITIZER.

CAUSES IRRITATION

TARGET ORGAN DATA

BRAIN AND COVERINGS (OTHER DEGENERATIVE CHANGES)

BEHAVIORAL (ANOREXIA, HUMAN)

BEHAVIORAL (CHANGE IN MOTOR ACTIVITY)

BEHAVIORAL (ATAXIA)

BEHAVIORAL (COMA)

LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)

GASTROINTESTINAL (NAUSEA OR VOMITING)

KIDNEY, URETER, BLADDER (CHANGES IN TUBULES)

EFFECTS ON FERTILITY (POST-IMPLANTATION MORTALITY)

EFFECTS ON FERTILITY (ABORTION)

EFFECTS ON EMBRYO OR FETUS (FETAL DEATH)

TUMORIGENIC EFFECTS (UTERINE TUMORS)

NUTRITIONAL AND GROSS METABOLIC (CHANGES IN: METABOLIC ACIDOSIS)

TUMORIGENIC (NEOPLASTIC BY RTECS CRITERIA)

TUMORIGENIC (TUMORS AT SITE OF APPLICATION)

And the following information was available from the NIH [emphasis added]:

***** National Toxicology Program, Chemical Repository of the National Institutes of Health (Revised as of August 13, 2001)*

*SAX TOXICITY EVALUATION:

THR: Poison by ingestion, subcutaneous, intravenous and possibly other routes. An experimental neoplastigen and teratogen. Experimental reproductive effects.

*CARCINOGENICITY: Tumorigenic Data: TDLo: scu-rat 104 mg/kg (1Y-I)

*OTHER TOXICITY DATA:

Skin and Eye Irritation Data: eye-rbt 8 ug MLD

Status: EPA Genetox Program 1988, Positive: S cerevisiae gene conversion

EPA TSCA Chemical Inventory, 1986 Human lethal dose: 2-4 grams [301]

*SYMPTOMS:

Symptoms of exposure to this class of compounds includes aphthous stomatitis, catarrhal gingivitis, nausea, liquid stools, pain, liver disorder, injury to the cardiovascular system and hematopoietic system, deafness and ataxia. Exposure may be fatal. Headache, paresthesia of the tongue, lips, fingers and toes, other non-specific dysfunctions, metallic taste, slight gastrointestinal disturbances, excessive flatus and diarrhea may occur. Acute poisoning may cause gastrointestinal irritation and renal failure. Early signs of severe poisoning include fine tremors of extended hands, loss of side vision, slight loss of coordination in the eyes, speech, writing and gait, inability to stand or carry out voluntary movements, occasional muscle atrophy and flexure contractures, generalized myoclonic movements, difficulty understanding ordinary speech, irritability and bad temper progressing to mania, stupor, coma, mental retardation in children, skin irritation, blisters and dermatitis [173]. Other symptoms include chorea, athetosis, tremors, convulsions, pain and numbness in the extremities, nephritis, salivation, loosening of the teeth, blue line on the gums, anxiety, mental depression, insomnia, hallucinations and central nervous system effects [301]. Exposure may also cause irritation of the eyes, mucous membranes and upper respiratory tract [269].

> And most recently, the CDC has published a compilation of studies demonstrating the toxicity of Thimerosal:
>
> ***** National Institute of Occupational Safety (NIOSH)'s Registry of Toxic Substances of the US Centers for Disease Control and Prevention (CDC) (Revised as of August 2006)*

P. It is also clear that an alternative preservative was available that Bayer should have used instead of Thimerosal --one that was actually available at the relevant times, one that was much safer and which would "truly provide more benefits than risks." This information was withheld from Plaintiffs and their health care providers. The FDA did NOT require the use of a highly dangerous product like Thimerosal, also known as Thiomersal and Merthiolate. Some examples of alternatives include the following:

> Lowe and Southern published in the peer-reviewed journal of *Letters in Applied Microbiology* in 1994 on, "The Antimicrobial Activity of Phenoxyethanol in Vaccines." These researchers reported (emphasis added), "The preservative most commonly used is thiomersal. Other preservatives are being evaluated because: (i) this material has become difficult to obtain; (ii) the use of mercury-containing compounds in medicinal products is considered potentially harmful; and (iii) it has been found that some vaccine components are unstable in the presence of this material (Davisson et al. 1956)." It is important to note that the researchers quote in support of their contentions a paper published in 1956 in the peer-reviewed *Journal of Laboratory and Clinical Medicine*.[14] These researchers describe that others have published in the peer-reviewed literature since the early 1960s on manufacturers using alternative preservatives other than Thimerosal. Specifically, these researchers published, "Some manufacturers have already used alternative preservatives…(Cameron 1974; Ajjan 1988)." They also stated, "The use of phenoxyethanol, in conjunction with antibiotics for preservation of poliomyelitis (Salk) vaccine was reported by Pivnick et al. (1964). The use of this combination in DTP-polio vaccine was reported by Cameron (1974)." In the present study, the researchers comparatively evaluated the activity of the antimicrobial preservatives, phenoxyethanol and Thimerosal. It was determined (emphasis added), "Both chemicals were equally effective in inactivating challenge doses of Gram-negative and Gram-positive micro-organisms, as well as yeast." In addition, these researchers reported regarding phenoxyethanol (emphasis added), "The antimicrobial

[14] Lowe, I., and Southern, J. 1994. The antimicrobial activity of phenoxyethanol in vaccines. *Lett. Appl. Microbiol.* 18:115-116.

action of phenoxyethanol has been studied by Gilbert et al. (1977a, b, c), and the mode of action in Gram-negative bacteria is reported to be due to the disruption of cell membrane integrity and uncoupling of oxidative phosphorylation…The low toxicity of phenoxyethanol in children has been reported by Marini and Vechatti (1955) who used up to 0.15 g Kg^{-1} body weight, as a solvent for intravenous penicillin with no reported adverse effects. The levels of phenoxyethanol used in our study would be equivalent to 2.5 mg per dose."

Hekkens et al. (1983) undertook an evaluation of the effectiveness of some preservatives in inactivated human vaccines by application of the test described in the United States Pharmacopoeia (USP) XIX.[15] These researchers described that 5 recommended strains as well as 3 strains isolated from vaccines were used as test strains. It was observed that vaccines preserved with Thimerosal did not fully meet the requirements for a vaccine preservative according to the criteria established by the USP XIX. By contrast, it was observed that the preservative, phenol, met the requirements of the USP XIX. Additionally, it was found phenoxyethanol had the potential to be an alternative preservative in vaccines.

Byatt and Henderson (1973)[16] reported (emphasis added), "(n)ine preparations of six antiseptic substances were applied to the perineum of pregnant women at term in order to assess their efficacy in sterilizing the skin. The efficacy, in descending order of effectiveness, after three minutes' exposure, was *p*-chlorm-*m*-xylenol in alcohol (surgical Dettol); chlorhexidine gluconate in detergent (Hibiscrub), followed by the aqueous preparations *p*-chlor-*m*-xylenol (Dettol), chlorhexidine gluconate (Hibitane), cetrimide (Cetavion), povidoneiodine (Disadine), benzalkonium chloride (Resiguard), and merthiolate." Overall, it was observed that a 0.1% Merthiolate solution in water was only associated with a 28% reduction bacterial cells. It is important to note that water (as a control) was associated with a 24% reduction in bacterial cells. By contrast, every other disinfectant tested other than Merthiolate produced greater than a 50% reduction in bacterial cells.

Q. Furthermore, numerous researchers have called for the end of the use of Thimerosal, also known as Thiomersal and Merthiolate, as a preservative. It is apparent that

[15] Hekkens, F. E. An., Polak-Vogelzang, A. A., and Kreeftenberg, J. G. 1983. The antimicrobial effectiveness of some preservatives in inactivated human vaccines. *J. Biol. Stand.* 9:277-285.
[16] Byatt, M. E., and Henderson, A. 1973. Preoperative sterilization of the perineum: a comparison of six antiseptics. *J. Clin. Pathol.* 26:921-924.

Bayer withheld such information from the FDA and from their package insert. Examples of this extensive literature include the following:

> Heyworth and Truelove (1979) undertook a study to evaluate the potential adverse effects of Thimerosal-containing immune globulin preparations.[17] These researchers found, "Merthiolate contains an ethyl group directly joined to a mercury atom. Organic compounds containing an alkyl radical directly attached to a mercury atom are more toxic to human subjects than are other types of mercury compounds. Considerable accumulation of mercury occurs in tissues of mice injected with ethyl mercury compounds, and in 1 human subject receiving intravenous infusions of Merthiolate-containing plasma tissue accumulation of mercury was also observed." The researchers went onto conclude (emphasis added), "(f)or many years, Merthiolate has been known to have anti-microbial activity. When it was first introduced as an anti-microbial preservative, little information about the fundamental biological effects of organic mercury compounds was available. We should like to suggest that Merthiolate should now be regarded as an inappropriate preservative for anti-lymphocytic globulin preparations and other materials which are intended for administration to human subjects."

> Matheson et al. (1980) published a case-report of mercury-poisoning induced-by long-term injection of Thimerosal-containing gamma globulin.[18] They found that the patient developed pink, scaling pruritic palms and soles, flushed cheeks, photophobia, irritability, a fine tremor, altered sensation in his fingertips, and slowed nerve conduction velocity. These authors reported, "(m)ost commercially available gammaglobulin preparations contain Merthiolate (sodium ethylmercurithiosalicylate), a mercury-containing compound, which serves as a bacteriostatic agent. Thus, patients receiving regular injection of gammaglobulin are potentially at risk for the development of mercury toxicity…It would appear, therefore, that Merthiolate which is used as a preservative in a commercially available gammaglobulin preparation represents a potential hazard to patients…"

> Forstrom et al. (1980) also published warnings regarding the use of Thimerosal, this time in vaccines (emphasis added), "…reactions can be expected in such a high percentage of

[17] Heyworth, M. F., and Truelove, S. C. 1979. Problems associated with the use of Merthiolate as a preservative in anti-lymphocytic globulin, *Toxicology* 12:325-333.

[18] Matheson, D. S., Clarkson, T. W., and Gelfand, E. W. 1980. Mercury toxicity (acrodynia) induced by long term injection of gammaglobulin. *J. Pediatr.* 97:153-155.

Merthiolate-sensitive persons that Merthiolate in vaccines should be replaced by another antibacterial agent."[19]

Heyworth (1982) described (emphasis added), "(d)uring a study of the properties of two antisera which had been prepared against human lymphoid cells, the present author found that one of the antisera was cytotoxic to lymphoid and non-lymphoid cells(.)…This effect was attributable to the organomercurial compound Merthiolate, which had been added to the (antilymphocyte serum) ALS as a preservative…In the opinion of the present author, Merthiolate should no longer be added to ALS or other materials which are intended for use in human subjects. Tissue accumulation of mercury has been observed…"[20]

Kravchenko et al. (1983) questioned the use of Thimerosal in vaccines and its inexplicable acceptance in light of mounting scientific evidence demonstrating its inherent toxicity.[21] These researchers found (emphasis added), "(o)ur experiments show that Merthiolate in 1:10,000 titer can not only damage cells in culture but also change their properties…Increased sensitivity to this mercury compound has been frequently noted in medical literature, and deserves particularly close attention. Although there are numerous clinical studies confirming Merthiolate's damaging action on humans, (medical and biological preparations) MBP preservation with it continues and is even recommended by WHO." In regard to the use of Thimerosal in vaccines, the researchers concluded (emphasis added), "(a)ll of the above show that Merthiolate usage for MBP manufacturing is inadmissible, especially in pediatrics….Vaccines must contain only specific substances, free of ballast. There is no way that cell damage can cause not harmful sequelae in the body."

Winship (1985) reported (emphasis added), "(m)ulti-dose vaccines and allergy-testing extracts contain a mercurial preservative, usually 0.01% Thimerosal, and may present problems occasionally in practice. It is, therefore, now accepted that multi-dose injection

[19] Forstrom, L., Hannuksela, M., Kousa, M., and Lehymuskallio, E. 1980. Merthiolate hypersensitivity and vaccination. *Contact Dermatitis* 6:241-245.

[20] Heyworth, M. F. 1982. Clinical experience with antilymphocyte serum. *Immunol. Rev.* 65:79-97.

[21] Kravchenko, A. T., Dzagurov, S. G., and Chervonskaia, G. P. 1983. Evaluation of the toxic action of prophylactic and therapeutic preparations on cell cultures. III. The detection of toxic properties in medical biological preparations by the degree of cell damage in the L132 continuous cell line. *Zh. Mikrobiol. Epidemiol. Immunobiol.* 3:87-92.

preparations are undesirable and that preservatives should not be present in unit-dose preparations."[22]

Stetler et al. (1985) from the US Centers for Disease Control and Prevention also evaluated the use of Thimerosal as a preservative in vaccines and found it to be unsatisfactory.[23] The authors reported that Thimerosal was ineffective as a vaccine preservative, and that giving more mercury than was present in a single Thimerosal-containing vaccine might pose a health hazard to vaccine recipients. Evaluating the effectiveness of Thimerosal as a preservative in vaccines, the authors stated (emphasis added), "(l)aboratory experiments in this investigation have shown up to 2 weeks' survival of at least one strain of group A Streptococcus in multidose DTP (Diphtheria-Tetanus-Pertussis) vials. The manufacturer's preservative effectiveness tests showed that at 4°C, 4.5% of the challenge Streptococcus survived 14 days after inoculation into a multi-dose DTP vaccine vial. At currently used concentrations, Thimerosal is not an ideal preservative." The authors also made specific reference to the toxicity of Thimerosal (emphasis added), "(h)owever, because Thimerosal is an organic mercurial compound, higher concentrations might reduce vaccine potency or pose a health hazard to recipients." Their recommendations regarding the use of multi-dose vials with a Thimerosal preservative were as follows (emphasis added), "(t)he Thimerosal preservative present in DTP vaccine requires substantial time to kill organisms and cannot be relied upon to prevent transmission of bacteria…Instead, the most important means of preventing abscesses secondary to DTP vaccination is to prevent contamination by careful attention to sterile technique."

Furthermore, Cox and Forsyth (1988) recommended (emphasis added), "(h)owever, severe reactions to thiomersal demonstrate a need for vaccines with an alternative preservative."[24]

Nascimento et al. (1990) not only reported on a death following Thimerosal ingestion but also warned of the widespread danger, which Thimerosal posed.[25] Specifically, they

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[22] Winship, K. A. 1986. Organic mercury compounds and their toxicity. *Adverse Drug React. Acute Poisoning Rev.* 5:141-180.

[23] Stetler, H. C., Garbe, P. L., Dwyer, D. M., Facklam, R. R., Ornstein, W. A., West, G. R., Dudley, J., and Bloch, A. B. 1985. Outbreaks of group a streptococcal abscesses following diphtheria-tetanus-toxoid pertussis vaccination. *Pediatrics* 75:299-303.

[24] Cox, N. H., and Forsyth, A. 1988. Thiomersal allergy and vaccination reactions. *Contact Dermatitis* 18:229-233.

[25] Nascimento, L. O., Lorenzi Filho, G., and Rocha Ados, S. 1990. Lethal mercury poisoning due to ingestion of Merthiolate. *Rev. Hosp. Clin. Fac. Med. Sao Paulo* 45:216-218.

reported (emphasis added), "…(a) case of mercurial poisoning caused by ingestion of an organic mercurial compound, Thimerosal, found in local antiseptic solutions. The clinical picture consisted of grave neurological symptoms which were not reversed by penicillamine and resin administration despite rapid plasma level reduction of mercury. We call attention to this case because of the widespread availability of antiseptic solutions containing mercurial compounds…"

Aberer (1991) reviewed the continued use of mercury in medicine.[26] In his article, Aberer (1991) was comprehensive in declaring the extent of the problem that Thimerosal represented in pharmaceutical products (emphasis added), "(t)he presence of mercury in over-the-counter drugs for the eye, ear, nose, throat, and skin; in bleaching creams; as preservative in cosmetics, tooth pastes, lens solutions, vaccines, allergy test and immuno-therapy solutions, in antiseptics, disinfectants, and contraceptives; in fungicides and herbicides; in dental fillings and thermometers; and many other products, makes it a ubiquitous source of danger." He then went on to document the systemic failure to remove this toxin from pharmaceutical products, "Despite calls for abandonment and a general prohibition in 1967, mercury is still listed in many pharmacopoeias, including that of the United States...Thus mercury is still much more frequently used than is generally believed. This seems incomprehensible because side effects are not only potentially disastrous but also numerous and well documented." In describing the numerous and well-documented side effects of the use of mercury in medicine, he stated that these included, "Neurologic and psychiatric symptoms, renal toxicity, erythroderma, and other signs of poisoning...", and furthermore, "(k)nowledge of all these side effects has been available for some time." He concluded by arguing (emphasis added), "(r)ecommendations not to use mercury salts in children or only on prescription are insufficient. Removal from textbooks seems overdue...However, calls for their abandonment (as early as 1960) or restricted use have not sufficed. Only a general ban and their removal from the pharmacopoeias will be effective in stopping the use of these dangerous, outmoded substances."

Additionally, Seal et al. (1991), in their article on the case against Thimerosal in the peer-reviewed journal *Lancet*, concluded that (emphasis added), "Thimerosal is a weak antibacterial agent that is rapidly broken down to products, including ethylmercury

[26] Aberer, W. 1991. Topical mercury should be banned-dangerous, outmoded, but still popular. *J. Am. Acad. Dermatol.,* 24:150-151.

residues, which are neurotoxic. Its role as a preservative in vaccines has been questioned, and the pharmaceutical industry considers its use as historical."[27]

R. In addition, others have documented the significant toxicity of Thimerosal (and its ethylmercury and inorganic mercury breakdown products), and the relative ineffectiveness of Thimerosal as an antimicrobial agent since the early 1930s, despite claims by Bayer to the contrary.

As early as Kharasch (1932) patent application on Thimerosal (Merthiolate)[28], Kharasch stated, "…I will describe my invention more specifically in connection with that one of such compounds which is now in most general use. That is sodium ethyl mercuri-thiosalicylate, which is known on the market as Merthiolate…" According to Kharasch (1932), when Thimerosal, "…is first made, it is entirely bland, both to the skin and mucous membrane. However, it is found that on standing…the solution loses its blandness and acquires certain burning properties; which make its use as an antiseptic and bactericide less desirable." In describing the chemical basis for Thimerosal's ability to acquire "certain burning properties," Kharasch (1932) detailed an important discovery regarding the decomposition products of Thimerosal. Kharasch (1932) recorded that if "…such for instance as for sodium ethyl mercuri-thiosalicylate, is allowed to stand, there is a dissociation of a few of the molecules at the bond between the sulphur and the ethyl mercury radical, producing a small quantity of resultant ions…" and that, "(h)owever, on account of the invariable presence of oxygen, and of a catalyst such as copper, the sulphur-containing ion…is oxidized to the di-thio compound…The formation of the di-thio compound removes these sulphur-containing ions from the…mixture…so that progressively more ionization of the alky mercuric sulphur compound occurs…This process results in an excess of the mercuri ions such as C_2H_5 -- Hg^{++} -- which react with the hydroxyl ions present in the solution to form C_2H_5 -- Hg^{++} -- ^{-}OH." Subsequently, Kharasch (1932) went onto describe in the patent that the C_2H_5 -- Hg^{++} -- ^{-}OH breakdown product of Thimerosal might mediate adverse reactions in humans. These observations are important because they demonstrate knowledge that Thimerosal would break down, in fairly rapid order, to produce ethylmercury hydroxide and thiosalicylate, and that the ethylmercury breakdown product was the one mediating Thimerosal toxicity.

[27] Seal, D., Ficker, L., Wright, P., and Andrews, V. 1991. The case against Thiomersal. *Lancet* 338:315-316.

[28] Kharasch, M. S. 1932. *Stabilized Bactericide and Process of Stabilizing it*. US Patent 1,862,896.

In 1935, some of the first serious safety concerns were raised regarding Thimerosal. Specifically, researchers reported a (emphasis added), "…reaction in about 50% of the dogs injected with serum containing dilutions of Merthiolate, varying in 1 in 40000 to 1 in 5000, and we have demonstrated conclusively that there is no connection between the lot of serum and the reaction. In other words, Merthiolate is unsatisfactory as a preservative for serum intended for use on dogs." They also noted, regarding the reactions observed in dogs following administration of Thimerosal-containing serums, "…in some instances, the reaction is extremely severe." It was concluded, "I might say that we have tested Merthiolate on humans and find that it gives a more marked...reaction than does phenol or tricresol".[29]

Additionally, Salle and Lazarus (1935) determined that Thimerosal was 35.3-times more toxic for embryonic cells than for the bacterial cells that Thimerosal was supposed to kill.[30]

Soon after this 1935 publication by Salle and Lazarus, Cummins (1937) documented in the literature the first reports of Thimerosal-induced poisonings in animal model systems. Specifically, he described (emphasis added), "…two sets of 7 flasks each were treated with an amount of Merthiolate varying in dilution from 1 to 100 to 1 in 10 million of the medium in each series…The guinea-pigs inoculated with 1 c.cm. of the mixtures after 24 hours all died; the first of Merthiolate poisoning…"[31]

Welch (1939), of the US FDA, expanded the evaluation of the toxic action of potential preservatives, including Thimerosal, in mammalian tissue culture experiments. Welch (1939), when comparing the relative toxicity of Thimerosal with other germicide compounds, determined that Thimerosal was, by several orders of magnitude, the most toxic compound tested.[32]

In addition, Welch and Hunter (1940), again of the US FDA, continued their previous research by reporting on the toxicity indices of germicides with human and guinea pig blood. The researchers determined the toxicity indexes for each germicide tested, by comparing the highest dilution producing inhibition in human cells or in guinea pig cells with the highest dilution that was bactericidal for Staphylococci. Their experiments showed that Thimerosal was, in fact, considerably more toxic for human cells than bacterial cells (toxicity

[29] Subcommittee on Human Rights and Wellness, Government Reform Committee (Chairman Dan Burton). 2003. *Mercury in Medicine – Taking Unnecessary Risks*. Washington, DC.
[30] Salle, A. J., and Lazarus, A. S. 1935. A comparison of the resistance of bacteria and embryonic tissue to germicidal substances. *Proc. Soc. Exp. Biol. Med*. 32:665-667.
[31] Cummins, S. L. (1937). Merthiolate in the treatment of tuberculosis. *Lancet* 230:962-963.
[32] Welch, H. 1939. Mechanism of the toxic action of germicides on whole blood measured by the loss of phagocytic activity of leucocytes. *J. Immunol.* 37:525-533.

index = 5.7). Furthermore, it was observed, among the 10 germicides tested, that Thimerosal had the ninth worst toxicity index.[33]

Kinsella (1941) described a cases-series of 13 patients with bacterial endocarditis that received Thimerosal treatment.[34] It was observed that all patients receiving the Thimerosal treatment died, and that following autopsy, some of the patients were determined to have died of mercury poisoning from the Thimerosal treatment. For example, one report recorded (emphasis added), "Female, aged 23. Onset: Sore throat treated with sulfanilamide. Later fever and pain the left chest. Examination: Systolic murmur second i.c.s left. Blood cultures: Non-hemolytic strep. 37 times 50 colonies per c.c. Clinical Diagnosis: Subacute bacterial endocarditis pulmonic valve (congenital). Treatment: Merthiolate. Autopsy: Healing pulmonary endarteritis – mercury poisoning." In light of determination the treatment with Thimerosal produced mercury poisoning in humans, the suggestion was made to significantly limit Thimerosal exposure in humans due to its toxicity and potential hazards.

Ellis (1943) published an article on the possible danger of using Thimerosal in ophthalmic ointments.[35] In his report evaluating this use of Thimerosal, Ellis (1943) observed, "…Merthiolate is capable of causing an inflammation of the mucous membrane in patients..." and made a very strong recommendation, based upon his clinical experience and that of several other physicians, considering the adverse effects of Thimerosal use. He disputed the acceptance of Thimerosal in medicine. Referencing the potential ability of Thimerosal to produce permanent damage in the patient during clinical use, Ellis proposed (emphasis added), "…it may be advisable to withdraw this product from the market…" It is important to note that this recommendation was made more than 6 decades ago, after Thimerosal had been on the market for only, approximately, 10 years.

Ellis (1947) continued his work on Thimerosal, and subsequently reported on an even larger case-series of patients experiencing adverse reactions following application of Thimerosal.[36] Based upon his further clinical experiences, as well as those of his medical colleagues, Ellis

[33] Welch, H., and Hunter, A. C. 1940. Method for determining the effect of chemical antisepsis on phagocytosis. *Am. J. Public Health* 30:129-137.
[34] Kinsella, R. A. 1941. Chemotherapy of bacterial endocarditis. *Ann. Intern. Med.* 15:982-986.
[35] Ellis, F. A. 1943. Possible danger in use of Merthiolate ophthalmic ointment. *Arch. Ophthalmol.* 30:265-266.
[36] Ellis, F. A. 1947. The sensitizing factor in Merthiolate. *J. Allergy* 18:212-213.

(1947) once again strongly rebuked those advocating the continued use of Thimerosal in clinical medicine, stating (emphasis added), "…it may be dangerous to inject a serum containing Merthiolate into a patient…"

Morton et al. (1948), under a grant from the Council on Pharmacy and Chemistry of the American Medical Association, published an article on the bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci. They reported (emphasis added), "…the label on a bottle of 'Solution Merthiolate, 1:1,000, Stainless' purchased as recently as June 1947 states that it is 'a stable, stainless, organic mercury compound of high germicidal value, particular in serum and other protein media.' It is not highly germicidal and especially does not possess high germicidal value in the presence of serum and other protein mediums. The loss of antibacterial activity of mercurials in the presence of serum proves their incompatibility with serum… The comparative in vitro studies on mercurochrome, metaphen and Merthiolate on embryonic tissue cells and bacterial cells by Salle and Lazarus cannot be ignored. These investigators found that metaphen, Merthiolate and mercurochrome were 12, 35 and 262 times respectively more toxic for embryonic tissue cells than for Staphylococcus aureus. Nye and Welch also found the same three mercurial compounds more toxic for leukocytes than for bacterial cells. Not only is there direct toxic action of the mercurial compounds on the cellular and humoral components of the animal body, but there is also the possibility of sensitization."[37]

Engley (1950) of the Biological Department, Chemical Corps, Camp Detrick published an evaluation of mercurial compounds as antiseptics and judged mercurials to be inadequate as antiseptics, "(m)ercurial compounds have not enjoyed a peaceful career as antibacterial chemicals since their popularization as germicides over sixty years ago (Kock, 1891)…During the ensuing years, other workers, using various techniques, have also shown that the antibacterial activity of mercurials is only slowly bactericidal and mainly bacteriostatic. This bacteriostasis is even nullified by the presence of many types of sulfur-containing compounds, including sulfides (Geppert, 1889), (Hunt, 1937), thioglycollate (Marshall, Gunnison, and Luxen, 1941), body fluids such as plasma (Johnson and Meleney, 1942), and other organic matter (Greeen and Birkeland, 1944)." Furthermore, and of even greater concern, was Engley's conclusion that mercurials, such as Thimerosal, "…are ineffective *in vivo* and may be more toxic for tissue cells than bacterial cells, as shown in mice (Nungester and Kempf, 1942) (Saber, 1942) (Spaulding and Bondi, 1947), tissue culture (Salle and Catlin,

[37] Morton, H. E., North, L L., and Engley, F. B. 1948. The bacteriostatic and bactericidal actions of some mercurial compounds on Hemolytic streptococci: in vivo and in vitro studies. *J. Am. Med. Assoc.* 136:37-41.

1947), and embryonic eggs (Witlin, 1942) (Green and Birkeland, 1944), and with leucocytes (Welch and Hunter, 1940)."[38]

Davisson et al. (1956) from the Lilly Research Laboratories reported on a molecular mechanism for Thimerosal induced cellular toxicity. Specifically, they described that the cellular toxicity of Thimerosal was the result of, "…partial ionization of the compound to go give a low but effective level of ethyl mercuri ion ($C_2H_5Hg^+$), which blocks enzymatic processes by combining with sulfhydryl groups on the enzymes."

Subsequently, Engley (1956) presented a paper to the 42nd midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago, Illinois.[39] Engley overtly questioned the acceptance of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating, "(t)he use of mercurials as preservatives in vaccines and antisera is of considerable interest. These chemicals are added to protect against the introduction of organisms in multi-use containers in particular. We have always wondered about their efficacy in that both vaccines and antisera contain reactive groups to tie up these compounds. In a series of continuing experiments over the past several years we have begun to evaluate various preservatives in serum and vaccines under conditions of use. Employing stock vaccines and serum with and without preservatives and stored at varying lengths of time a contaminating dose of representative sporeformer (*Bacillus subtilis*) in the spore stage gram negative rod (*E. coli*) and gram positive coccus (*S. aureus*) were added. While the mercurial preservatives had good activity on initial addition, after storage of three, six or more months decreasingly less to negligible residual activity appeared to be left, indicating that the chemical was tied up by the protein of the biological or otherwise inactivated. A check on a series of over one thousand bottles of various biologicals from clinics obtained after use revealed that up to five percent contained micro-organisms. This would suggest that once these biologicals are in the hands of users a problem still exists. Regarding preservatives, one of the real problems existing in hospitals and clinics is the need for good preservatives in the routine eye dilators and nasal preparations of the decongestant type. Routine checks of these indicate a high percentage of contaminated solutions. In one instance we had direct evidence of upper respiratory cross-infection from the use of a common nasal dropper preparation in a clinic."

Engley (1956) then gave an evaluation of the relative toxicity of mercurials, such as Thimerosal, by stating, "(t)he toxicity of chemicals used as drugs on or in the body has been of considerable interest since man first began exposing himself to various chemicals many years ago. Unfortunately there have not been good techniques for toxicity determinations

[38] Engley, F .B. 1950. Evaluation of mercurial compounds as antiseptics. *Ann. N. Y. Acad. Sci.* 53:197-206.

[39] Engley, F. B. 1956. *Mercurials as Disinfectants: Evaluation of Mercurial Antimicrobic Action and Comparative Toxicity for Skin Tissue Cells*. Chicago, IL: 42nd Mid-Year Meeting of the Chemical Specialties Manufacturer's Association.

of certain types of chemicals which might be really indicative of toxicity for humans...Graph 15 compares mercurial compounds and shows how they fit in with other compounds in toxicity...Mercurochrome appears to be the least toxic ranging down through Merthiolate...One point should be made here. Bichloride of mercury has always been pointed out as an extremely toxic mercurial and the organic mercurials were supposed to be much less toxic but according to these data we find bichloride right in the middle of the organic mercurials in regard to cell toxicity ... mercurial antiseptics proved to be more toxic than the antibiotics in common usage..." Finally, it should be noted, with respect to the toxicity experiments undertaken by Engley (1956), that he determined Thimerosal was significantly toxic to human tissue culture cells at a concentration of 10 parts-per-billion.

Nelson and Gottshall (1967) from the Division of Biologic Products, Bureaus of Laboratories, Michigan Department of Public Health published (emphasis added), "(p)ertussis vaccines preserved with 0.01% Merthiolate are more toxic for mice than unpreserved vaccines prepared from the same parent concentrate and containing the same number of organisms…An increase in mortality was observed when Merthiolate was injected separately, before or after an unpreserved saline suspension of pertussis vaccine."[40]

From 17-19 June 1971, an international conference and its associated advisory committee reviewed the environmental toxicity from mercurials.[41] One of the key areas examined at this conference was the metabolic fate of ethylmercury salts, with a specific emphasis on Thimerosal, in humans. That committee reported, "(t)he toxic nature of ethylmercury has been considered to be fairly similar to that of methylmercury salts. In the recommendations of the international committee on Maximum Allowable Concentration for mercury and its compounds, ethylmercury was grouped with methylmercury. Reports on human intoxication with ethylmercury salts have usually reported symptoms similar to those of methylmercury, which is accentuated by the typical neurological symptoms, although there have been a few reports that noted slightly different symptoms from the typical features of methylmercury poisoning. In acute experiments on animals, ethylmercury has an LD_{50} similar to that of methylmercury salts and a high neurotoxicity similar to that of methylmercury." In addition, its report stated, "(b)y using methods for estimating the inorganic and total mercury content of biological specimens, the metabolism of

[40] Nelson, E. A., Gottshall, R. Y. 1967. Enhanced toxicity for mice of pertussis vaccines when preserved with Merthiolate. *Appl. Microbiol.* 15: 590-593.

[41] Suzuki, T., Takemoto, T. L., Kashiwazaki, H., and Miyama, T. 1973. Metabolic fate of ethylmercury salts in man and animals. In: *Mercury, Mercurials, Mercaptans*. Miller, M. W., and Clarkson, T. W. eds. Springfield: Charles C. Thomas, pp 209-240.

ethylmercury salts was studied in man and animals. The (carbon-mercury bond) C-Hg of ethylmercury salts was able to break fairly rapidly and to a great extent in men, who were patients and were transfused with a commercial product of human plasma containing 0.01% (Thimerosal) sodium ethylmercurithiosalicylate, and also in mice injected subcutaneously or intravenously with ethylmercurithiosalicylate solution. The increasing level of inorganic mercury and its percentage to total mercury content in the brain were quite distinguishable with post-injection time in mice, which resulted in longer biological half-time of total mercury than that reported for methylmercury injection."

Gasset et al. (1975), under a grant from the US National Institutes of Health, examined mercury distribution following administration of Thimerosal to animals.[42] They stated (emphasis added), "(a) comparison of topical and subcutaneous administration of Thimerosal to rabbits shows that a substantial concentration of mercury was present in blood and tissues of the treated animals and their offspring. Thimerosal was found to cross the blood-brain and placenta barriers." These researchers also determined that administration of Thimerosal caused a dose-dependent significant increase in fetal mortality.

Blair et al. (1975) also examined mercury distribution and form following administration of Thimerosal to animals.[43] In 1975, the authors reported that squirrel monkeys were dosed intranasally with saline or Thiomersal (sodium ethylmercurithiosalicylate, 0.002% w/v) daily for 6 months. The total amounts of Thiomersal given during the 6 month period were 418 µg (low dose group) and 2280 µg (high dose group). This was equivalent to 207 µg mercury and 1125 µg mercury. The dose differential was achieved by more frequent administration to the high dose group. Mercury concentrations were significantly raised over control values in brain, liver, muscle and kidneys, but not blood. Concentrations were highest in kidneys, moderate in liver and lowest in brain and muscle. Much of the mercury was present in the inorganic form (37-91%).

These researchers considered regarding persistent low-level elevations of mercury in the brain (emphasis added), "…it is conceivable that insidious damage may occur at lower concentrations…Damage to only a few cells may be not detect in the clinical investigation

[42] Gasset, A. R., Itoi, M., Ishii, Y., and Ramer, R. M. 1975. Teratogenicities of ophthalmic drugs. 2. Teratogenicities and tissue accumulation of Thimerosal. *Arch. Ophthalmol.* 93:52-55.
[43] Blair, A. M. J. N., Clark, B., Clark, A. J., and Wood, P. 1975. Tissue concentrations of mercury after chronic dosing of squirrel monkeys with Thiomersal. *Toxicology* 3:171-176.

because other cells take over. Clinical effects do show up early when too many cells have been damage in a short time. However, over a long period, even a low frequency of brain cell damage, above the natural inactivation of these cells, has an effect on the organism as the number of cells for each brain function is limited. Such damage may have serious effects in the later stages of life. These considerations must be kept in mind when the toxicological evaluation of alkyl mercury compounds is made. Perhaps any increase in brain mercury should be viewed as potentially hazardous. Increases in brain levels of mercury in the high dose group were found following thiomersal administration. The mercury present in the brain was mainly ionic which may be the more toxic form of mercury." The authors concluded (emphasis added), "…accumulation of mercury from chronic use of thiomersal-preserved medicines is viewed as a potential health hazard for man."

The US Veterans Administration and the US National Institutes of Health funded research published by Van Horn et al. (1977) that examined the toxic effects of Thimerosal on human tissue culture cells.[44] These authors commented, "(w)idespread use of the mercurial-containing preservative Thimerosal as an antibacterial agent in ophthalmic drugs and solutions warranted an investigation into its possible cytotoxic effects on the functional and ultrastructural integrity of the corneal endothelium…(scanning electron microscopy) SEM and (transmission electron microscopy) TEM of the endothelium of corneas perfused with 0.0005 percent Thimerosal for 5 hours revealed condensed mitochondria, cytoplasmic vacuoles, and cytoplasmic flaps at the apical end of the cellular junctions. Perfusion of higher concentrations (0.001 and 0.005 percent) of Thimerosal in (glutathione bicarbonate Ringer's solution) GBR resulted in increases in corneal thickness after 2 hours and irreversible ultrastructural damage to the endothelial cells by 5 hours. Corneas perfused with 0.01 and 0.1 percent Thimerosal in GBR showed a rapid and immediate increase in corneal thickness and endothelial cell death and necrosis within 1 hour. It is postulated that the mercury in Thimerosal becomes bound to the cell membrane protein sulfhydryl groups, causing an increase in cellular permeability. These results suggest that the prolonged exposure of the corneal endothelium to Thimerosal in the accepted antimicrobial dosage of 0.005 to 0.001 percent may result in functional and structural damage to the endothelium…It is therefore concluded that ophthalmic solutions containing Thimerosal should not be used…"

[44] Van Horn, D. L., Edlehauser, H. F., Prodanovich, G., Eiferman, R., and Pederson, H. J. 1977. Effect of ophthalmic preservative Thimerosal on rabbit and human corneal endothelium. *Invest. Ophthalmol. Visual Sci.* 16:273-280.

Parry (1977) utilized yeast cultures for the detection of environmental mutagens using a fluctuation test.[45] He described (emphasis added), "(a) microbial fluctuation test, modified for the detection of environmental mutagens has been evaluated using a number of strains of the yeast *Saccharomyces cerevisiae*. Auoxtrophic diploid cultures of yeast which produce prototrophic colonies by both mitotic gene conversion and mutation have been extensively utilized for the detection and evaluation of chemicals showing genetic activity. A number of the yeast strains utilized were shown to be suitable for use in the fluctuation test…The yeast strains respond to doses of mutagens at least a 100-fold lower than that required in a conventional short exposure treat and plate experiment. In experiments involving the induction of mitotic gene conversion at the tryptophan-5 and histidine-4 loci in the flucuation test significant increases in prototrophic cells were produced in the presence of…the preservative Thiomersal (0.0001 µg/mL)…The results demonstrate that the fluctuation test provides an extremely sensitive assay for the detection of chemicals which show genetic activity in yeast at non-toxic concentrations." It should be noted that Parry (1977) observed Thimerosal induced significant genetic alterations in yeast cells at a level < 1 part-per-billion.

Fagan et al. (1977) published a case-series of children who were apparently poisoned by Thimerosal.[46] Fagan et al. (1977) reported, in a study funded by the National Institute of Environmental Health Sciences of the US National Institutes of Health, that between 1969 and 1975, 13 cases of exomphalos were treated by Thimerosal. The authors analyzed the mercury content in tissues from 10 of the patients who had died. Upon reviewing the test results, the researchers stated (emphasis added), "(t)he results showed that Thiomersal can induce blood and organ levels of organic mercury which are well in excess of the minimum toxic levels in adults and fetuses…Although Thiomersal is an ethyl mercury compound, it has similar toxicological properties to methyl mercury and the long-term neurological sequelae produced by the ingestion of either methyl or ethyl mercury-based fungicides are indistinguishable." The authors also emphasized (emphasis added), "…the fact that mercury readily penetrates intact membranes and is highly toxic seems to have been forgotten. Equally effective and far less toxic broad-spectrum antifungal and antibacterial…antiseptics are currently available."

[45] Parry, J. M. 1977. The use of yeast cultures for the detection of environmental mutagens using a fluctuation test. *Mutat. Res.* 46:165-176.

[46] Fagan, D. G., Pritchard, J. S., Clarkson, T. W., and Greenwood, M. R. 1977. Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Arch. Dis. Child.* 52:962-964.

The FDA undertook a comprehensive review of the safety and effectiveness of over-the-counter (OTC) medicines in 1974. As one facet of this review, a panel of experts was assembled to review the safety and efficacy of OTC drugs containing mercury. The Advisory Review Panel on OTC Miscellaneous External Drug Products began its slow-paced review in 1975. In 1980, the FDA's Advisory Review Panel on OTC Miscellaneous External Drug Products finally delivered its report to the FDA. It reviewed 18 products containing mercury and found them all either unsafe or ineffective for their stated purpose of killing bacteria to prevent infections. In terms of effectiveness, the panel stated, "mercury compounds as a class are of dubious value for anti-microbial use." They also stated, "mercury inhibits the growth of bacteria, but does not act swiftly to kill them." In fact, the panel cited a study, conducted in 1935, on the effectiveness of Thimerosal in killing staphylococcus bacteria on chick heart tissue. The study determined that Thimerosal was 35-times more toxic to the heart tissue it was meant to protect than to the bacteria it was meant to kill. In terms of safety, the panel cited a number of studies demonstrating the highly allergenic nature of Thimerosal and related organic mercury products. For example, it cited a Swedish study that showed that 10% of school children, 16% of military recruits, and 18% of twins, and 26% of medical students had hypersensitivity to Thimerosal. They stated that while organic mercury compounds, like Thimerosal, were initially developed to decrease the toxicity of the mercury ion, Thimerosal was actually found to be more toxic than bi-chloride of mercury for certain human cells. By way of summary, "(t)he Panel concludes that Thimerosal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin, and its allergy potential. It is not effective as a topical antimicrobial because its bacteriostatic action can be reversed."[47]

Royhans et al. (1984) reported on mercury toxicity following pediatric Thimerosal ear irrigations.[48] With regard to the danger posed by mercurials, the researchers were expansive in stating (emphasis added), "(a)lthough aqueous Merthiolate has been used for years as a topical antiseptic, a recent review of its use by the Food and Drug Administration resulted in its classification as 'less than effective.' Furthermore, two of the ingredients (Thimerosal and borate) in Merthiolate are toxic if absorbed or injected...Symptoms of organic mercury poisoning chiefly involve the central nervous system, including paresthesia of the mouth, lips, tongue, and extremities; speech disorders, with difficulty in articulating words; difficulty in swallowing; salivation; neurasthenia; inability to recall basic information; emotional instability; ataxia; clumsiness; stupor; and coma…Reactions to mercury depend to a large extent on the form of the chemical agent; its absorption, storage, and excretion;

[47] Subcommittee on Human Rights and Wellness, Government Reform Committee (Chairman Dan Burton). 2003. *Mercury in Medicine – Taking Unnecessary Risks*. Washington, DC.
[48] Rohyans, J., Walson, P. D., Wood, G. A., and MacDonald, W. A. 1984. Mercury toxicity following Merthiolate ear irrigations. *J. Pediatr.* 104:311-313.

duration of exposure; and individual susceptibility. Both inorganic and dissociable organic mercurials appear to act by the same mechanism. Mercury ion reacts with sulfhydryl groups to form mercaptides, which inactivate sulfhydryl enzymes and interfere with cellular metabolism…The blood-brain barrier, is also more permeable to organic than inorganic mercury. There are definite individual differences in sensitivity to the effects of mercurials. Some patients tolerate prolonged exposure without symptoms; others have significant systemic signs and neurological disability with much less exposure. The mercury in Merthiolate is a thiosalicylate compound that is converted to inorganic mercury more rapidly than is methyl mercury. The organic compound itself is also easily absorbable, and undergoes widespread tissue distribution. Toxicity may be related both to the biotransformation into inorganic mercury and to the unchanged compound, both of which cause degenerative changes in the brain, especially in the visual cortex and cerebellum, and proliferative changes throughout the cerebellar cortex."

Withrow and his colleagues (1989), from the US Food and Drug Administration, in keeping with the expanding circle of scientists and physicians expressing ever-increasing concerns in regard to the use of Thimerosal as a preservative, evaluated the cytotoxicity and mutagenicity of Thimerosal at preservative levels in a tissue culture system.[49] These researchers reported, "(i)t is known that Thimerosal…present in lens care solutions sometimes cause(s) ocular irritation in contact lens users. For example, Coward et al. (1984) reported that 33% of patients using lens care solutions with Thimerosal…experienced solution intolerance…In vitro studies have shown that preservatives are toxic to cultured human and rat corneal epithelial cells and toxic to isolated rabbit corneas, and to intact rabbit eyes." Additionally, these researchers described the impact of Thimerosal at the cellular level (emphasis added), "(c)ell survival and mutagenesis were measured using the L5178Y mouse lymphoma (TK +/-) system. Cells were exposed to varying amounts of preservatives for 1 h at 37°C, and then aliquots were irradiated with UVA radiation (during the exposure to the preservative). Cells were then assayed for survival, and for mutagenesis at the thymidine kinase (TK) locus. In concentrations commonly found in ophthalmic solutions…Thimerosal (was) toxic to cells, and Thimerosal was slightly mutagenic. When cells were exposed to preservative and UVA radiation…the mutagenic activity of Thimerosal was enhanced."

[49] Withrow, T. J., Brown, N. T., Hitchins, V. M., and Strickland, A. G. 1989. Cytotoxicity and mutagenicity of ophthalmic solution preservatives and UVA radiation in L5178Y cells. *Photochem. Photobiol.* 50:385-389.

III. LEGAL ARGUMENT

INTRODUCTION

Bayer's motion raises the purely legal questions of whether the FDA regulatory process for biologic products preempts plaintiffs' state claims as a matter of law. FDA approval and license of Bayer's Thimerosal-containing HypRho-D product and its approval of the product label does not as a matter of law preempt Plaintiffs' state common law claims. Congress did not intend that the federal regulatory program for biologics would displace tort claims under state law; in fact, the FDA regulatory scheme and the civil justice system are complementary processes to promote drug safety and public health.

Congress has purposely declined to preempt civil lawsuits involving failure-to-warn claims against drug companies; the weight of judicial decisions historically rejects FDA preemption arguments; and nothing about the FDA's recent "Preemption Preamble"[50] changes the analysis—this Court is not required to defer to the FDA's gratuitous and self-serving attempt to override Congressional intent and the tort law of the states.

POINTS AND AUTHORITIES

Plaintiffs' Claims are not Preempted Because Congress has Not Expressed an Intention to Prohibit Drug Product Liability Lawsuits, and the FDA Cannot "Interpret Away" Substantive State Tort Law.

[50] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biologic Products (21 C.F.R. parts 201, 314 and 601),* 71 Fed. Reg. 3922, 3933-36 (Jan. 24, 2006).

Overview of Preemption Law.

The Supreme Court has identified three types of preemption: express preemption, field preemption, and conflict preemption. *English v. General Elec. Co.,* 496 U.S. 72, 78-79 (1990). Express preemption exists when Congress clearly states its intent to preempt state law. *Id.* at 78. Field preemption arises where congress has intended the federal government to occupy an entire field of regulation exclusively, leaving no room for states to supplement federal law. *Id.* at 79. Conflict preemption displaces state law to the extent that it actually conflicts with federal law. *Id.*

Bayer does not argue that express or field preemption applies here, because Congress neither explicitly intended for the Food, Drug and Cosmetic Act ("FDCA") to displace state tort law, nor has Congress expressed any intent for the FDCA to govern drug safety exclusively. Therefore, conflict preemption is Bayer's sole allegation in this case.

Conflict preemption, which may be "direct" or "indirect," applies only if it is impossible for a private party to comply with both state and federal requirements. Indirect conflict occurs only where state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.* (citations omitted). Neither conflict exists in this case. Given the Constitution's reliance on federalism and respect for state sovereignty, there is a strong presumption that Congress does not cavalierly eradicate state law causes of action. *Bates v. Dow Agrosciences, LLC,* 544 U.S. 431, 449 (2005). As the Supreme Court has emphasized, "[I]n areas of traditional state regulation, we assume that a federal statute has not supplanted state law unless Congress has made such an intention 'clear and manifest.'" *Id.* (citations omitted) In other words, a court should presume that the state's historic police powers and

common law remedies are not to be superseded by a federal act unless it was the clear and manifest purpose of Congress to do so. *New York State Conference of Blue Cross & Blue Shield Plans v. Travelers Ins. Co.,* 514 U.S. 645, 655 (1995).

The presumption against preemption is especially strong if it would effectively deny Plaintiffs a remedy, which is precisely what Bayer wants to do. The Supreme Court has emphasized that a preemptive federal regulatory scheme that would leave injured citizens without any federal or state recourse runs counter to the fundamental principles of justice. *Sprietsma v. Mercury Marine,* 537 U.S. 51, 64 (2002) (noting that it would be irrational for Congress to preempt common law claims that provide an important remedy for compensating accident victims); *Silkwood v. Kerr-McGee Corp.,* 464 U.S. 238, 251 (1984). As the Supreme Court recently noted:

"The long history of tort litigation against manufacturers of poisonous substances adds force to the basic presumption against preemption. If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly."

554 U.S. 431, at 449.

Thus, courts should be extremely reluctant to imply "clear evidence" of the intent to immunize an entire industry from liability, even a highly regulated one. *Ohler v. Purdue Pharma, L.P.,* CV-01-3061, 2002 WL 88945 at *14 (E.D. La. Jan. 22, 2002). Such intent can be ascribed only under the most compelling circumstances. *English v. General Elec. Co.,* 496 U.S. 72, 87-90 (1990). Because the displacement of the state law protecting the health and safety of their citizens is not favored, a party seeking preemption of state law bears a heavy burden of proof.

In the context of FDA preemption, one court has noted, "Congress knows how to enact FDA legislation that contains a preemption clause. Thus, the absence of any such clause with respect to prescription drugs demonstrates an implied intent not to preempt cases, such as this." *Cartwright v. Pfizer,* 369 F. Supp. 2d. 876, 885 (E.D. Tex. 2005).

Bayer also contends that gratuitous commentary the FDA recently inserted in its introduction to new labeling rules automatically immunizes the entire pharmaceutical industry against liability in cases arising from state tort law, regardless of what Congress intended.[51] The effect is to deprive plaintiffs in this litigation of all legal recourse, since the FDCA does not provide remedies for damages to injured parties. This Court should deny the motion, because there is no evidence that Congress so intended. An agency cannot unilaterally extinguish state law claims, at least where there is no express grant of power from Congress to do so.

Courts have Consistently Denied Preemption Involving Prescription Drug Cases, Holding that FDA Prescription Drug Labeling Requirements are Minimum Standards.

The issue of whether FDA approval is a shield to liability in failure to warn and defective design and testing cases has been addressed in the Eastern District of Pennsylvania, in a vaccine injury case, in which Judge Ditter soundly rejected the vaccine maker's attempt to argue that regulation of vaccine labels under the FDCA and the Vaccine Act preempted the tort claims of a vaccine-injured child. Addressing arguments very similar to those raised by defendants in this case involving a vaccine additive, Judge Ditter held that:

> . . . mere compliance with an FDA suggestion, or for that matter, rule or order, does not mean that state tort law becomes irrelevant. First, compliance with an FDA regulation may establish that the manufacturer met the appropriate minimum

[51] Bayer Motion at p. 14-18.

> standards of due care, but compliance does not absolve the manufacturer of all liability. Manufacturers must meet state safety requirements, whether codified or embodied in the common law, in addition to satisfying the initial FDA requirements.

Mazur v. Merck & Co., 742 F. Supp. 239, 247 (E.D. Pa. 1990) (internal citation omitted). The opinion further notes that the state tort system is "intended to supplement federal regulation by providing a vehicle for compensation of vaccine-related injuries." *Id.*

Judge Ditter's conclusion is consistent with opinions in other jurisdictions. *See, e.g., Hill v. Searle Laboratories*, 884 F.2d 1064, 1068 (8th Cir. 1989) ("FDA regulations are generally minimal standards of conduct unless Congress intended to preempt common law, which Congress has not done in this area."); *Wells v. Ortho Pharmaceutical Corp.*, 788 F.2d 741, 746 (11th Cir. 1986)\ ("An FDA determination that a warning is not necessary may be sufficient for federal regulatory purposes but still not be sufficient for state tort law purposes."); *Brochu v. Ortho Pharms. Corp.*, 642 F.2d 652, 658 (1st Cir. 1981) (FDA approval of a drug label is not conclusive in a common law failure to warn action); *Kociemba v. Searle & Co.*, 680 F. Supp. 1293, 1299 (D. Minn. 1988); *Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085, 1092 (C.D. Cal. 2000), *rev'd on other grounds*, 358 F.3d 659 (9th Cir. 2004).[52]

In addition, manufacturers such as Bayer are not locked into a particular drug label or warning. In fact, FDA regulations allow manufacturers to change label language if supported by research (largely provided by the manufacturers), and manufacturers can make changes and later ask for FDA approval. *Jackson v. Pfizer, Inc.*, 432 F.Supp.2d 964, 965 (D. Neb. May 31, 2006)

[52] The FDA preemption defense has recently received judicial attention in a number of cases involving anti-depressant drugs in district courts around the country, and has been the case with pharmaceutical cases generally, the overwhelming weight of authority in recent these cases holds that state law warning claims are not preempted by the FDA's regulation of the product. *See, e.g., Laisure_Radke v. Par Pharmaceutical, Inc.,* 426 F. Supp.2d 1163, 1169 (W.D. Wash. 2006); *Witczak v. Pfizer,* 377 F.Supp.2d 726, 728-30 (D. Minn. 2005); *Cartwright v. Pfizer,* 369 F. Supp.2d 876, 881 (E.D. Tex. 2005); *Peters v. Astrazeneca, LP,* 417 F. Supp.2d 1051, 1055 (W.D Wis. 2006); *McNellis v. Pfizer*, CV-05-5500, 2005 WL 3752269 *10 (D. N.J. December 29, 2005).

(citing 21 C.F.R. §314.70(c)(6)(ii)(A). This ability of manufacturers to seek changes to the product labels—including changes in response to a jury finding that the existing warnings are inadequate—shows that a manufacturer "could meet both federal and state law requirements," obviating any conflict. *Mazur,* 742 F.Supp. at 248 (citing 21 C.F.R. §601.12).

The poor record of the "FDA preemption defense" in the case law is to be expected given Congress' treatment of preemption in the regulation of pharmaceuticals. Long before federal law regulated drugs, states provided redress to people harmed by drugs and other products through their laws and tort systems, and Congress recognized the states' traditional role in protecting the health and safety of their citizens. When Congress enacted the Food, Drug & Cosmetic Act (FDCA) of 1938, it rejected the creation of a federal private right of action for damages caused by unsafe products because this cause of action already existed under state common law.[53] Similarly, when Congress amended the FDCA in 1962, Congress again made clear that it did not intend to invalidate state law, by establishing an extremely high burden on anyone attempting to argue that a state law conflicted with the federal regulations:

> Nothing in the amendments made by this Act to the Federal Food, Drug and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provisions of state law.

Pub.L. No. 87-781, 76 Stat. 780, 793 (1962). Given this, it is not surprising that *no* appellate court has found that Congress intended the FDCA to preempt common law tort claims. Bayer falls far short of meeting its burden of showing that Virginia law is in "direct and positive

[53] Adler & Mann, *Preemption and Medical Devices: The Courts Run Amok,* 59 Mo. L. Rev. 895, 924 & n. 130 (1995).

conflict" with the FDA's regulatory program, and Glaxo thus cannot overcome the extremely strong presumption against preemption.

The Recent FDA "Preemption Preamble" is Neither Binding nor Persuasive, and Should be Given no Deference.

Bayer tries to exploit the FDA's recent opinion language about preemption in the recent new drug label rules (71 Fed.Reg. 3933-35 (Jan. 24, 2006)), and apparently hopes that this will turn the judicial tide on the issue—that through administrative fiat the FDA might provide liability protection where the Congress and the judiciary have not. Bayer's enthusiasm is premature and misplaced.

First, the "Preemption Preamble" is entitled to little deference because it contradicts the FDA's official position, articulated until 2001, that the agency's proposed changes to the label rules would not conflict with or preempt existing state law. In 1988, the FDA stated in a regulatory preamble addressing medication guides that agency regulations establish the minimal standards necessary; state tort law did not conflict with the agency's regulations. 63 Fed.Reg. 66378-01, 66384 (Dec. 1, 1988). In 2000, the FDA said the proposed label rule changes would:

> Establish minimum graphical requirements for labeling. This proposal would also eliminate certain unnecessary statements on prescription drug labels and move other, less important information to labeling. Because enforcement of these labeling provisions is a Federal responsibility, there should be little, if any, impact from this rule, if finalized, on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of Government. ***In addition, this rule does not preempt State law***.

65 Fed.Reg. 81082, 81103 (2000) (emphasis added). An agency's interpretation of its regulations is not given its usual deference when the interpretation "contradicts the agency's own previous construction" of the regulation, if courts have relied on the previous construction as

authoritative. *Norfolk Southern Railway Co. v. Shanklin*, 529 U.S. 344, 356 (2000). Here, the FDA's apparent flip-flop on the preemption issue obliges the Court to discount any deference that might have been due to the FDA opinion. While an agency reversal of position may be granted some deference if the agency provides a compelling reason explaining the change, Bayer points to no such persuasive rationale proffered by the FDA. The sudden "about face" by the agency is therefore entitled to very little judicial deference.

In addition, the FDA position is not persuasive because in adding this language, the FDA failed to comply with its own requirements to: 1) involve the states in the rule-making proceedings prior to a preemption decision; 2) keep regulatory preemption to a minimum level; 3) consult with state officials to minimize the conflict between agency decisions and state law; and 4) provide state and local officials with notice and an opportunity to participate in the rule-making process. 432 F. Supp.2d at 968, fn.3 (internal citations omitted).

A number of District Courts have decided FDA preemption issues in the months since the agency promulgated the rule in January 2006 (it became effective in June 2006) and, as was the case before January 2006, the current of judicial opinion has run against the FDA's interpretation and against the manufacturers' attempts to use the preamble to shield industry from liability. *Jackson,* 432 F. Supp.2d at 964; *Laisure_Radke,* 426 F. Supp.2d at 1169; *Peters,* 417 F. Supp.2d at 1055. In the Eastern District of Arkansas, Judge Wilson simply adopted by reference in its entirety Judge Bataillon's *Jackson v. Pfizer, Inc.* opinion in an order denying Wyeth's preemption motion in the hormone therapy Multi-District Litigation, finding that Judge Bataillon's holding was "mules and bicycles;" that is, directly on point. At least one state court trial judge has also considered and rejected the preamble preemption argument, in an unpublished opinion. *Coutu v. Tracy,* Case No. C.A. PC-00-3720 (Sup. Ct. R.I., May 11, 2006) .

Chief Judge Harvey Bartle III of the E.D. PA rejected Wyeth's FDA preemption arguments in a diet drug case, allowing plaintiff's design defect claim to proceed. *Mingus v. Wyeth, et al.,* MDL Docket No. 1203, Case No. CV04-23744 (April 21, 2006), at p. 7.

Plaintiffs' Claim that Bayer Negligently Failed to Adequately Test the Thimerosal used in its Product is Not Preempted.

As one of their specifications supporting their design defect and negligence claims, Plaintiffs properly allege that Bayer should have conducted more and better testing of the Thimerosal in its products so that a safer product would be marketed, and so that proper warnings could be given. Bayer's failure to conduct adequate testing is but one of several reasons that a potentially toxic product was approved by the FDA and marketed. Just as FDA licensing and label approval does not, as a matter of law, preempt plaintiffs' claims altogether, the FDA approval process does not, as a matter of law, establish the standard of care under state law nor does it excuse the standard of care required by state tort law. FDA approval does not foreclose a factual finding that Bayer could and should reasonably have conducted addition product testing, because the FDA approval process establishes minimum standards, not maximum standards. *Hill,* 884 F.2d at 1068 ("FDA regulations are generally minimal standards of conduct unless Congress intended to preempt common law, which Congress has not done in this area.").

Nothing about the states' imposition of additional or heightened standards of care for product design or labeling conflicts with the FDA regulatory program; it is entirely possible for a manufacturer such as Bayer to comply with both minimal FDA standards and higher standards established under state law. *Mazur,* 742 F. Supp. at 247. The complementary role of the tort

system thus advances the important public policy goal of allowing the states to exercise their traditional role of protecting the public health of their citizens. *Id.*

Plaintiffs allegations that Bayer failed to adequately test their Thimerosal-containing products are not preempted by the mere fact that the FDA approved the product and its label, and Bayer's motion should therefore be denied.

Plaintiffs' "Alternative Packaging" Claims are not Preempted.

Plaintiffs allege that Bayer could have used a safer alternative product design by packaging the biologic without the use of Thimerosal. While the FDA required the use of *some* preservative in Bayer's single-dose presentations of the product, the FDA did not specifically require Thimerosal as the *only* preservative option. In fact, the FDA mandate to use preservatives in biologics also required that any preservative used must be non-toxic in the dose administered. The toxicity of Thimerosal is one of the fundamental fact questions in this case, and neither the FDA requirement for a preservative, nor the FDA approval of Thimerosal for this product for a period of time establishes that Thimerosal was sufficiently nontoxic as required in 21 C.F.R. Sec. 610.15(a) for Thimerosal used as a preservative in biological drug products.

Whether safer alternative preservatives were available to Bayer at the time it manufactured and marketed the HypRho-D product is a question of fact for resolution after discovery. It is not a question that can be answered as a matter of law in, and Bayer's motions should therefore be denied.

Plaintiffs are not Suing to Enforce FDA Regulations

Plaintiffs claim that Bayer's Thimerosal-containing products were unsafe, that Bayer knew or should have known that the Thimerosal used in its product was unsafe, and that Bayer failed to warn of the dangers of Thimerosal. These claims against Bayer rely in part on allegations that Bayer, while completing and submitting its paperwork for FDA approval, did not pass on to the FDA material and relevant information about the safety and effectiveness of Thimerosal, or, as required by FDA regulation, toxicological proof that Thimerosal was sufficiently nontoxic in the formulation of their drug product to the child developing in the womb. Plaintiffs do not dispute that Bayer submitted material to the FDA in order to obtain product licenses and label approval. Plaintiffs contend that the information was inadequate, incomplete, or inaccurate, based on the toxicity of Thimerosal and the availability of safer ways to package FDA-compliant biologics.

Bayer mischaracterizes the claims as a private action to enforce FDA regulations. That is not the case, the claims are not preempted by the FDA's regulatory program, and the motion should be denied.

Bayer's Motion is Premature

Plaintiffs have not been allowed any discovery in these proceedings to date. Plaintiffs have moved this Court for leave to amend their complaint and for leave to add other defendants. It is respectfully requested that the Court grant these motion and allow discovery at this time. A motion for judgment on the pleadings is premature at this time.

Federal Rule of Civil Procedure 12(b)(6) provides that a court may dismiss a complaint "for failure to state a claim upon which relief can be granted." In deciding a motion to dismiss under Rule 12(b)(6), all allegations in the complaint must be taken as true and viewed in the light most favorable to the plaintiff. Warth v. Seldin, 422 U.S. 490, 501, 95 S. Ct. 2197, 45 L. Ed. 2d 343 (1975); Trump Hotels & Casino Resorts, Inc. v. Mirage Resorts, Inc., 140 F.3d 478, 483 (3d Cir. 1998).

Exhibit B attached hereto is a thoughtful analysis and commentary from the former Commissioner of the FDA, David Kessler. He concludes:

> The point of this essay is not to denigrate the job the FDA does in protecting consumers. The talented and dedicated men and women who work at the FDA do an admirable job with the tools they have been given. But those tools are imperfect, and the FDA cannot, at least at this point, effectively safeguard our nation's drug supply on its own. In an ideal world, the FDA would have immediate access to data enabling it to pinpoint problems as they emerge, the personnel and other resources needed to deal effectively and swiftly with emerging hazards, and the insulation from political and other forces that often seek to apply pressure to influence agency decision-making. In the meantime, however, we believe it would be a mistake to broadly preempt state-law failure-to-warn cases, which impose a complementary discipline on the marketplace, prompt disclosure of safety information that is not otherwise available to the FDA and the public, and provide redress for consumers injured through no fault of their own.

Plaintiffs respectfully request that Bayer's motion be denied, so that Wesley can seek the redress that is available to a citizen of Virginia for the injuries he has suffered, through no fault of his own, but rather because of the negligence and breach of warranties of Bayer .

Respectfully submitted
this 17th day of January, 2008.

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CERTIFICATE OF SERVICE

I herby certify that on the 17th day of January, 2008, I will electronically file the foregoing with the Clerk of Court using the *CMlECF* system, which will then send notification of such filing to the following:

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